Notice of Allowability	Application No.	Applicant(s)	
	10/725,405	ANGRES ET AL.	
	Examiner	Art Unit	
	Raymond J Henley III	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *Applicants' Amendment and Declaration under 1.131 filed November 26, 2004*.

2. ☒ The allowed claim(s) is/are *1-24*.

3. ☐ The drawings filed on _____ are accepted by the Examiner.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *12282004* .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

A SINGLE Document

RAYMOND HENLEY III
PRIMARY EXAMINER
AU 1614

EXAMINER'S REASONS FOR ALLOWANCE/AMENDMENT

Amendment

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Isaac Angres on December 28, 2004. The amendments made to claims 13 and 24, *infra*, are made without prejudice. Applicants reserve the right to file one or more applications containing claims directed to the aspect of the claimed subject matter that is being deleted from the present claims, i.e., the prevention of atherosclerosis.

The application has been amended as follows:

In the Claims:

In claims 6-10, line 1, after "claim 1", ---wherein--- has been inserted.

In claim 13, lines 1-2, "or prevention" has been deleted.

In claim 21, last line, ---, wherein said combination includes (a) at least one inhibitor of HMG CoA reductase and (b) a compound that inhibits cholesterol synthesis at a point between the formation of acetate and mevalonate--- has been inserted after "mevalonate".

In claim 24, line 3, "or prevent" has been deleted.

Reasons for Allowance

For the reasons set forth in the amendment filed November 26, 2004 at pages 9-12, all issues raised by the Examiner in the previous Office action dated May 26, 2004 have been overcome and thus are withdrawn.

An updated search by the Examiner has revealed Laguana Granja et al. (U.S. Patent No. 5,856,316, "Laguana"). For the following reasons, the claims are deemed patentable over the teachings of Laguana which is deemed the closest, applicable art. The following "Reasons for Allowance" is deemed necessary because Laguana is newly cited and the Examiner wishes to make the record complete.

Applicants' invention is directed to pharmaceutical compositions comprising (a) an HMG CoA reductase inhibitor and (b) a compound that inhibits cholesterol synthesis at a point between the formation of acetate and mevalonate as well as to methods of treating a disorder related to elevated serum cholesterol levels which comprise the administration of said composition to a subject in need thereof.

Claim 1 is representative of compositions of the invention and reads:

1.(original) A pharmaceutical composition comprising:

(a) an effective amount of HMG-CoA reductase inhibitor; and

(b) an effective amount of a compound that inhibits cholesterol synthesis at a point between the formation of acetate and mevalonate.

Claim 21 is representative of the methods of the invention and reads, with the above amendment indicated therein:

21. (original) A method for treating a disorder related to elevated serum cholesterol concentration in a mammalian subject, comprising administering to the subject a therapeutically effective amount of a combination of a cholesterol biosynthesis inhibitor selected from the group consisting of HMG CoA reductase inhibitors and a compound that inhibits cholesterol synthesis at a point between the formation of acetate and mevalonate, wherein said combination includes (a) at least one inhibitor of HMG CoA reductase and (b) a compound that inhibits cholesterol synthesis at a point between the formation of acetate and mevalonate.

Laguana teaches pharmaceutical compositions comprising a mixture of primary aliphatic alcohols of 22 to 38 carbon atoms, a.k.a., "policosanol" or "a compound that inhibits cholesterol synthesis at a point between the formation of acetate and mevalonate", and various pharmaceutically acceptable carriers, including polyethylene glycol (see present claim 13) which is useful in a method treating hypercholesterolemia in animals, including humans (see the abstract; col. 3, Tables 1-3; and col. 3, line 63 – col. 4, line 12). Laguana further discloses that HMG-CoA reductase inhibitors were known to be useful for treating hypercholesterolemia (see col. 5, lines 25-51).

However, a combination of policosanol and an HMG-CoA reductase inhibitor and its subsequent use in a method for treating hypercholesterolemia is not taught or suggested by Laguana. In particular, one of ordinary skill in the art would appreciated from Laguana that because of the side effects of HMG-CoA reductase inhibitors, policosanol should be used instead of such inhibitors and not, as is presently claimed, in addition to such inhibitors.

In this regard, Laguana teaches:

"There are different commercial lipid-lowering drugs considered as effective, safe and well tolerated, but most of them produce different adverse side effects. Since lipid-lowering therapy must be administered chronically, this aspect is very important."(col. 4, lines 57-61).

Also, concerning HMG-CoA reductase inhibitors specifically, Laguana discloses:

"Lovastatin is the first of the "statins", drugs acting as inhibitors of HMG CoA-reductase and thus efficiently reducing serum cholesterol and LDL-C levels, it also moderately increases HDL-C and decreases triglycerides. Several adverse effects have been reported for this drug. Thus, the main adverse effects are miopathy (sic), mild to moderate increases of creatinphosphokinase and persistent increases in serum transaminases, that frequently became reversible after withdrawal of the treatment. Miopathy (sic) has occurred mainly in patients receiving concomitant therapy with inmunosuppresive (sic) drugs as gemfibrozil or niacin. Moreover, adverse effects such as skin rash, pruritus, headache and severe muscular lesions in sensitive patients resulting in myolisis (sic) have also been reported by lovastatin-treated patients. Moreover, drug-related occurrence of testicular atrophy and hepatic tumors in laboratory animals has been reported.

Similar, simvastatin and pravastatin are other "statins", acting by the same mechanism of lovastatin and showing approximately the same cholesterol-lowering effects. Adverse effects reported by these patients are similar to those reported for lovastatin-treated patients, but claimed as slightly lower. Simvastatin and pravastatin-treated patients reported constipation, flatulence, nausea, headache, fatigue, subcutaneous rash and myopathies affecting creatin-phosphokinase." (col. 5, lines 26-51).

Given the tenor of the above teachings of Laguana, it is the Examiner's position that one of ordinary skill in the art would find a combination of a HMG-CoA reductase inhibitor and policosanol unsatisfactory for the purposes of treating hypercholesterolemia and thus Applicants' invention is not taught or suggested by Laguana. "If [the] proposed modification would render the prior art invention...unsatisfactory for its intended purpose, then there is **no suggestion or motivation** to make the proposed modification."(emphasis added). See MPEP 2143.01 and *In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984).

Further, because one of ordinary skill in the art would more likely than not consider using those drugs having the fewest side effects possible, the Examiner considers the above teachings of Laguana tantamount to a teaching away from the presently claimed subject matter which

further supports the Examiner's conclusion that the claimed subject matter is allowable. "A *prima facie* case of obviousness may also be rebutted by showing that the art, in **any** material respect, teaches away from the claimed invention."(emphasis added). See *In re Geisler*, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997).

Accordingly, for the above reasons, claims 1-24, all of the claims in the application, are deemed allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Raymond J Henley III whose telephone number is 571-272-0575. The examiner can normally be reached on M-F, 8:30 am to 4:00 pm Eastern Time.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Raymond J Henley III
Primary Examiner
Art Unit 1614

December 28, 2004